

Critique of the Clinical Importance of Diuretic-Induced Hypokalemia and Elevated Cholesterol Level

One of the disappointing conclusions of the antihypertensive drug trials is that, while most morbid events were prevented by treatment, the incidence of death from coronary heart disease (CHD) was not significantly reduced. As originally emphasized in the Veterans Administration trial¹ and in most subsequent trials, treatment has not resulted in a significant reduction in myocardial infarction (MI) and sudden death.

See also pp 2648 and 2677.

Various hypotheses have been advanced to explain the lack of benefit in the prevention of complications of coronary heart disease, including the following: (1) critical reduction of blood flow in the coronary arteries by lowering blood pressure too far with antihypertensive drugs; (2) initiation of treatment too late in patients with extensive coronary artery atherosclerosis; (3) failure to reduce other risk factors, such as diet and cigarette smoking; (4) inadequate length of follow-up to detect differences; and (5) use of drugs that may increase the risk of CHD complications.

The last of the above hypotheses proposed that thiazides, which were used in all of the clinical trials, may increase the incidence of complications related to CHD. This hypothesis is based, on the one hand, on the assumption that thiazide-induced hypokalemia predisposes to severe and sometimes fatal arrhythmias^{2,3} and on the other hand that long-term elevation of cholesterol level by thiazides aggravates and accelerates coronary atherosclerosis. The first supposition is based mostly on two types of evidence: (1) primarily retrospective data from a few selected clinical trials and (2) a minority of the studies concerned with monitoring of the electrocardiographic (ECG) changes after the use of diuretics. The second, or cholesterol, argument also is based on a selected and incomplete review of the relevant literature.

The intracellular concentration of potassium normally is many times higher than the extracellular concentration because of cell-membrane metabolic pumps that actively extrude sodium but retain potassium inside the cells.⁴ There-

fore, the extracellular concentration may bear little relationship to the intracellular potassium content. Furthermore, factors other than thiazide treatment, including alkalosis and, especially, catecholamines, also may produce extracellular hypokalemia.

Thiazide-induced hypokalemia reflects only the extracellular and not the intracellular concentration of potassium. After reviewing the literature, Kassirer and Harrington⁵ concluded that after short-term or long-term treatment with thiazide diuretics, less than 5% of intracellular potassium is lost from the body, which is physiologically unimportant. The loss of body potassium is not progressive, as intake and output come back into balance after a few days despite continued treatment with diuretics.⁶

The electrical potential across a cell membrane is governed largely by the Nernst equation, which relates the electromotive force (voltage) to the ratio of the concentration of single types of positive ions inside the cell to that outside. Low potassium ion concentration in the extracellular fluid increases the negativity of the resting membrane potential (hyperpolarization), which acts as a stabilizer and reduces membrane excitability.⁷ Theoretically, therefore, except possibly in the presence of digitalis⁸ and reduced magnesium, which influence the sodium-potassium membrane pump, diuretics should increase the electrical stability of heart muscle cells and thus decrease the incidence of cardiac arrhythmias.

The hypothesis that fatal CHD is induced by diuretics has been advanced by several reviewers^{9,10} (see below). If so, the evidence from most clinical trials should indicate that the incidence of fatal CHD among thiazide-treated patients would be greater than that in those given other treatments. If such an excess of fatal CHD is not found in the diuretic-treated patients, then this is good evidence that thiazide-induced hypokalemia is not the cause of fatal MI or sudden death.

Thus far, in hypertension, 12 multiclinic morbidity-mortality trials have been published in which a thiazide diuretic was used either alone or as part of one of the therapeutic regimens (Table 1). Only 3 of the 12 trials observed a higher CHD mortality with diuretic treatment than with alternative regimens. Of these 3 trials, the most quoted is a subgroup of the Multiple Risk Factor Intervention Trial (MRFIT).³

Trial	No. of Patients	Diuretic & Dose, mg	All CHD Events		Fatal CHD	
			Thiazide	Other	Thiazide	Other
Trials Associating Thiazides With Increased CHD Risk						
MRFIT (ECG abnormal) ³	2478†	Chlorthalidone; hydrochlorothiazide, 50	29.2‡	17.7
Oslo trial ¹⁴	747	Hydrochlorothiazide, 50	20§	13	6§	2
Maphy ¹⁶	3234	Hydrochlorothiazide, 50-100; bendroflumethiazide, 5-10	43	36
Trials Indicating Thiazides Do Not Increase CHD Risk						
EWPHE ¹⁸	840	Hydrochlorothiazide, 25-50; triamterene, 50-100	12§	23
MRC ¹⁹	17354	Bendroflumethiazide, 10	5.2§	5.5	2.5§	2.3
Veterans Administration (90-114 mm Hg diastolic) ¹	380	Hydrochlorothiazide, 100	11¶	13	6¶	11
Australian ²⁰	3427	Chlorothiazide, 500-1000	70¶	68	2¶	8
Public Health Service ²¹	785	Hydrochlorothiazide, 50	8¶	7	2¶	2
HDFP ²²	10940#	Chlorthalidone, 25-100	131 ¶	148
HAPPY ¹⁷	6569	Bendroflumethiazide, 5; hydrochlorothiazide, 50	9.5§	10.6	4.1	4.4
IPPPSH ²⁰	6372	... ^{**}	...††
MPPCD (Helsinki, Finland) ²⁴	1203	Hydrochlorothiazide, 50‡‡

*MRFIT indicates Multiple Risk Factor Intervention Trial; ECG, electrocardiogram; MAPHY, Metoprolol Atherosclerosis Prevention in Hypertension study (a subgroup of the Heart Attack Primary Prevention in Hypertension [HAPPHY] trial; see text for details); EWPH, European Working Party on High Blood Pressure in the Elderly; MRC, Medical Research Council of Great Britain; HDFP, Hypertension Detection and Follow-up Program; IPPPSH, International Prospective Primary Prevention Study in Hypertension; and MPPCD, Multifactorial Primary Prevention Trial of Cardiovascular Disease in Middle-Aged Men.

†Subgroup with baseline ECG abnormality among 12 888 total patients.

‡Per 1000 patients.

§Per 1000 person-years of observation.

¶Total of deaths due to myocardial infarction plus other ischemic heart disease.

||Number of events.

#Total patients. See text for analysis of subgroups with and without resting ECG abnormalities.

**Randomized to receive placebo or oxprenolol, but diuretics were soon added in 67% of the oxprenolol group and 82% of the placebo group.

††Numerical data were not given, but "no significant association . . . between diuretic usage and cardiovascular events."²³

‡‡Coronary events tended to be accumulated in subgroups treated with β -blocking agents or clofibrate but there were few in those receiving probucol or diuretics.

CRITIQUE OF MRFIT SUBGROUP STUDY

For the study group as a whole, there was no essential difference in CHD mortality between the special intervention group, who received more thiazides, and the usual care (UC) group, who received less diuretics. It was only when subgroups were analyzed that were not part of the original randomization scheme that differences appeared between the special intervention and usual care groups. It is well known that retrospective, multiple subgroup analyses often lead to spurious results. The particular subgroup that cast suspicion on the diuretics consisted of the patients who exhibited minor resting ECG abnormalities on admission. The authors themselves were reserved in commenting on their findings. They pointed out some of the weaknesses of this kind of evidence and noted that the difference in CHD mortality even in the subgroup was not statistically significant and should be regarded only as a working hypothesis.

Other problems with the MRFIT data relating to this subject include the following: diuretics were prescribed in both the special intervention group and the usual care control group. Either chlorthalidone or hydrochlorothiazide was prescribed for 56% of the patients in the special intervention group and for 33% of those in the usual care group. Thus, nearly two thirds as many controls receiving usual care as patients in the experimental special intervention group were receiving diuretics. The MRFIT investigators explained this discrepancy by noting that the doses of hydrochlorothiazide used in the usual care group averaged less than that in the special intervention group. However, 53% of those taking diuretics in the usual care group were receiving 50 mg of

hydrochlorothiazide per day, a dose that is not considered small by today's standards. Also, in the patients with ECG abnormalities in the special intervention group, there was no trend toward greater mortality with the higher doses of diuretic than with the lower doses, nor was there any association in the special intervention group between CHD mortality and hypokalemia. In fact, such a relationship was not found in any of the published trials.

Another paradoxical aspect of the MRFIT subgroup with baseline resting ECG abnormalities is the distribution of risk between the special intervention and usual care groups. It is well known that the risk of CHD events is greater in hypertensive patients with ECG abnormalities than in those with normal ECGs. This difference was seen in the hypertensive patients in the special intervention group, where those with ECG abnormalities exhibited almost twice as many CHD deaths (29.2 per 1000) as those with normal baseline ECGs (15.8 per 1000).

Among the patients receiving usual care, however, the risk was not as expected. As pointed out by Papademetriou,¹¹ the hypertensive patients with baseline resting ECG abnormalities in the usual care group had a lower risk (17.7/1000) than did the patients with normal ECGs in the usual care group (20.7/1000). Both of the usual care subgroups received essentially the same medical management by outside physicians, and, therefore, the favorable result in the usual care groups with ECG abnormalities could not be ascribed to differences in treatment. Indeed, there is no apparent explanation for the abnormally low incidence of CHD events in the patients with resting ECG abnormalities in the usual care group. Thus, the

difference between the special intervention and usual care subgroups with ECG abnormalities was not due so much to an unexpectedly high rate of CHD deaths among the special intervention group as it was to an unexpectedly low rate among the usual care subgroup and, therefore, probably was not due to a toxic effect of the diuretic among patients receiving special intervention.

Furthermore, in the retrospective exercise ECG substudy of MRFIT,¹² the results were opposite to those of the retrospective resting ECG abnormalities substudy. An abnormal exercise ECG also suggests underlying CHD. Patients in the usual care group with exercise ECG abnormalities exhibited a 57% higher rate of CHD deaths than occurred in patients with similar exercise ECG abnormalities in the special intervention group ($P = .002$). This highly significant and opposite difference was in contrast to the baseline resting ECG abnormalities subgroup, in which the difference was not statistically significant.

Rautaharju and Neaton⁹ subjected the ECG records of MRFIT to computer analysis. The principal findings were similar to those obtained by visual inspection, that is, there was a higher risk of CHD mortality in the men with resting ECG abnormalities in the special intervention group than in the usual care group. They again found a significant increase in mortality among men in the usual care group showing positive ischemic exercise ECG responses. The computer analysis, therefore, contributed little new information to the original report.

Kuller et al¹⁰ presented the nonfatal incidence of MI in MRFIT. Among those with baseline resting abnormalities, the rates were 51 per 1000 in the special intervention group and 50 per 1000 in the usual care group, ie, no essential difference. They also found no relationship to dose of diuretic or to most recent level of serum potassium. In addition, they reviewed the relationship between serum potassium level and CHD mortality. As expected, serum potassium levels were lower in men in the special intervention group than in the usual care group. However, contrary to expectation, special intervention participants who died of CHD had higher average serum potassium levels at their last visit to the clinic than did surviving participants at comparable visits. After reviewing the MRFIT data in general, Kuller et al concluded that the evidence implicating the diuretics was still incomplete and further work was needed.

Cohen et al¹³ found an increase in the frequency of ventricular premature contractions (VPCs) associated with reduced serum potassium levels. These results are open to question, however, because they were based on readings of the brief recordings of the routine ECG. This method is no longer considered valid for assessing arrhythmic activity and has been replaced by the much more reliable 24- and 48-hour monitor methods.

OTHER TRIALS CONFIRMING MRFIT

The Oslo (Norway) trial¹⁴ reported a higher death rate in the thiazide-treated patients than in the non-thiazide-treated patients (Table 1). This was a small study that had 747 patients randomized and only six deaths due to CHD. Because of the small number of CHD events, these results must be regarded with caution. The Oslo group also reported their incidence of CHD events in the even smaller number of patients with minor baseline ECG abnormalities.¹⁵ Nonfatal CHD events, such as nonfatal MI and angina pectoris, were included. The actual incidence of combined CHD morbidity and mortality among patients with baseline resting ECG abnormalities was eight patients with CHD events in the thiazide-treated group compared with five in the placebo group. The difference was not significant, and with such a low

incidence of events, any interpretation with respect to treatment effects becomes questionable.

The MAPHY (Metoprolol Atherosclerosis Prevention in Hypertension) study¹⁶ reported a higher CHD mortality with thiazide diuretics than with β -blocker. Over a median follow-up of 4.2 years, the investigators found a significantly lower total mortality in metoprolol tartrate- compared with thiazide-treated patients, mostly due to fewer deaths from CHD and stroke. The problem in interpreting these results, however, is that the patients in the MAPHY study were a subgroup of those in the HAPPHY (Heart Attack Primary Prevention in Hypertension) trial (see below). Participating centers in the HAPPHY trial were divided into two groups. One group gave metoprolol, the other atenolol. Both groups could give either bendroflumethiazide or hydrochlorothiazide as the compared regimen. The HAPPHY trial¹⁷ found no difference in mortality in either fatal or nonfatal CHD events between diuretic-treated patients and those receiving one of two β -blockers, metoprolol or atenolol. The incidence of CHD events was, in fact, slightly higher in the total β -blocker group. Although the metoprolol subgroup (MAPHY trial) continued for an additional 13 months, the data indicated that for at least 6 years before the end of the study there was significantly greater protection against CHD events with the β -blocker ($P < .05$) than with the diuretic. The differing results of the parent (HAPPHY) and subgroup (MAPHY) trials can only be explained by a higher incidence of CHD events and strokes in the atenolol subgroup as compared with thiazides to counterbalance the results of the MAPHY or metoprolol subgroup. However, results in the atenolol subgroup were not described separately. Until this discrepancy is clarified, the conclusions of the MAPHY study that β -blockers are more effective than thiazides must be regarded with reserve.

TRIALS FAILING TO CONFIRM MRFIT

The remaining nine trials demonstrated either essentially the same or an actual decrease in the incidence of fatal MI and sudden death among the thiazide-treated patients (Table 1). In the study of the European Working Party on High Blood Pressure in the Elderly,¹⁸ the number of deaths due to CHD in the hydrochlorothiazide-treated patients was approximately half that found in the controls. These patients also received triamterene, and so it is possible that the favorable result may have been associated with prevention of hypokalemia. However, this seems doubtful because, as was referred to above, no association between CHD mortality and hypokalemia has been observed in any of the trials. The other studies reported below did not routinely prescribe potassium supplements.

The large Medical Research Council of Great Britain (MRC) trial randomized patients into three groups, to receive thiazides, propranolol hydrochloride, and placebo. They reported an essentially equal number of events due to CHD in the thiazide and placebo groups.¹⁹ The incidence of stroke, however, was reduced 69% in the thiazide-treated patients and 27% in the propranolol-treated patients compared with the placebo-treated patients. Propranolol failed to reduce overall CHD events significantly except in nonsmokers. The International Prospective Primary Prevention Study in Hypertension (IPPPSH) trial (described below) found a similar positive relationship between cigarette smoking and cardiac events among smokers in men receiving β -blockers but with an opposite trend in women.²⁰ However, the HAPPHY trial did not find a difference in the effect of β -blockers compared with diuretics in cigarette smokers as opposed to nonsmokers.¹⁷

The original Veterans Administration trial¹ exhibited a trend toward lower CHD mortality among thiazide-treated patients than placebo-treated patients that was not signifi-

cant, although the incidence was small.¹ There was also a trend for the incidence of fatal MI to be lower in the diuretic-treated patients in the Australian trial.²¹ In the Public Health Service Hospitals trial,²² the incidence of MI was small but was the same in the thiazide and placebo groups. The Hypertension Detection and Follow-up Program (HDFP) had the highest incidence of coronary deaths of any trial.²³ There were 51 fatal CHD events in the thiazide-treated, stepped-care patients as compared with 69 in the referred care group, that is, the incidence of fatal CHD was less in the stepped-care, thiazide-treated than in referred-care patients. The control group of this trial was managed similarly to that of the MRFIT; some of these patients received diuretics after being referred to outside medical facilities while others did not.

The three most recent trials also lend no support to the MRFIT claim of possible thiazide cardiotoxic effects. As described above, the HAPPHY trial¹⁷ involving 6669 randomized patients divided between diuretic and β -blockers found that morbidity and mortality rates for CHD were nearly identical for the total diuretic and total β -blocker groups. The incidence of diabetes also did not differ between thiazides and β -blockers.

The IPPPSH originally was a trial of propranolol vs placebo.²⁴ However, other drugs were added and a large proportion of the patients also received diuretics (Table 1). The authors noted that, "The IPPPSH results suggest that inclusion of diuretics as prescribed in this trial is not associated with excess cardiac risk."

Over a 5-year follow-up period, the Multifactorial Primary Prevention Trial of Cardiovascular Disease in Middle-Aged Men²⁵ found that the incidence of CHD events was significantly higher in the patients receiving β -adrenergic receptor blocking agents or clofibrate than in the untreated control group or in patients receiving probucol or diuretics. Thus, their findings were contradictory to the hypothesis that diuretics increase the risk of MI and sudden death.

DIURETICS AND SUDDEN DEATH

In the subgroup of MRFIT with minor baseline ECG abnormalities, a higher percentage of sudden death was found in the special intervention group than in the usual care group, although the difference was not significant.⁸ However, a strongly opposite trend was found in the subgroup with baseline exercise ECG abnormalities, the incidence of sudden death being nearly four times higher in the usual care group as in the special intervention group.¹²

The other trials reporting the incidence of sudden death per se are few. They include three small trials (the Veterans Administration study,¹ the Oslo study,¹⁴ and the Public Health Service trial²²) as well as the much larger but less well-controlled IPPPSH trial.²⁶ The first three smaller trials reported on a total of 11 patients with sudden death in the placebo groups and exactly the same number among the thiazide-treated patients. Interpretation of the results of the IPPPSH trial is difficult because the original randomization was to β -blocker vs placebo. However, thiazide diuretics were added in 67% of the β -blocker-treated patients and 82% of the placebo group. Potassium-sparing diuretics were used in 40% of all diuretic-treated patients. The incidence of sudden death was the same, with 36 patients in each group, in spite of the higher percentage of thiazide-treated patients in the placebo group. From the rather small amount of data available, therefore, there was little evidence to support the hypothesis that diuretics are a cause of sudden death.

COMPARISON OF MRFIT AND HDFP

The HDFP study group undertook a retrospective comparison similar to that of the MRFIT, comparing their patients

with minor baseline resting ECG abnormalities and those with normal baseline ECGs.²² Although the methods were similar, the findings were different from the MRFIT results. For the 1963 participants who had resting ECG abnormalities at baseline, mortalities for all major cardiovascular diseases and for all causes were significantly lower in the stepped care group (aggressive treatment with thiazide) than in the referred care group (partially thiazide treated). The CHD mortality was slightly higher in the stepped care group than in the referred care group in white men, but the low incidence of 11 deaths in the stepped care group vs 7 in the referred care group could have resulted from chance alone, as the authors state. An excess of CHD deaths in the stepped care as compared with the referred care group did not occur in black men. The problem was further compounded by the difficulties in ascertaining accurate causes of death, particularly among patients in the referred care group. These authors concluded that their data "offer no support for the hypothesis raised in MRFIT that interim diuretic therapy may increase the cardiovascular mortality rate in hypertensive patients with resting ECG abnormalities."

The results of 8.3 years of follow-up of patients in the HDFP, which is an extension of the original 5-year study, have recently been published.²⁸ After 8.3 years there were 16% fewer CHD deaths among the stepped care than among the referred-care group.

ECG MONITORING OF THIAZIDE TREATMENT

What are the effects of thiazides on the frequency and severity of ventricular arrhythmias? Hollifield and Slaton²⁷ were the first to report an increase in ventricular arrhythmias during exercise after treatment with thiazide diuretics. However, their work has not been confirmed by more recent studies. Bause, Fleg, and Lakatta²⁸ studied 68 hypertensive patients treated for a period averaging 4.5 years under maximal aerobic stress compared with an age-matched, untreated, normotensive control group. While they observed a higher incidence of isolated atrial and ventricular premature complexes in the diuretic-treated patients, they did not see any difference in frequent or complex supraventricular or ventricular premature beats. They concluded that, "Patients with uncomplicated hypertension treated with chronic diuretic monotherapy do not appear to be at increased risk for major arrhythmias during aerobic exercise." Papademetriou et al²⁹ carried out similar exercise studies in 10 patients with uncomplicated hypertension, twice while they were receiving placebo and 3 and 12 weeks after administration of 100 mg of hydrochlorothiazide per day. Diuretic treatment did not increase ventricular ectopy during exercise.

Holland et al³⁰ used 24-hour ECG monitoring but did not take into account the marked day-to-day variability in arrhythmic activity. The number of VPCs spontaneously fluctuates markedly from one day to the next, with variations from less than five to more than 30 VPCs per hour being not uncommon.³¹ Holland et al selected for study only those patients who exhibited less than six VPCs per hour at the baseline monitoring and rejected patients who exhibited more frequent VPCs. Because of day-to-day variability and regression toward the mean, they thereby increased the likelihood of recording greater ventricular arrhythmic activity on the second monitoring (which was also the postdrug recording).

The most extensive studies using ECG monitoring of the changes in hypertensive patients after use of thiazide diuretics have been carried out by Papademetriou and his associates.³² Without selecting hypertensive patients on the basis of the number of VPCs in their pretreatment ECG recordings, they carried out 24- to 48-hour monitoring before and 4

weeks after administration of hydrochlorothiazide, 50 mg twice daily, in 44 patients of whom 28 developed hypokalemia. There was no significant difference in arrhythmias before or after hydrochlorothiazide administration. These negative results have been confirmed by Lief et al³⁸ and Madias et al.³⁴ Papademetriou et al³⁵ also normalized the hypokalemia with potassium replacement therapy without altering ventricular arrhythmic activity. In addition, they monitored hypertensive patients with left ventricular hypertrophy before and after use of diuretics and again noted no change in 24-hour ventricular activity.³² More recent studies, therefore, fail to confirm the results of earlier investigators and indicate that thiazides do not increase ventricular arrhythmic activity regardless of whether they produce hypokalemia.

Caralis et al³⁶ monitored 16 patients before and after treatment with thiazides. Eight patients with no clinical evidence of heart disease had no change in ventricular ectopy during thiazide therapy. Eight other patients had rather severe and sometimes multiple cardiac complications, including 4 with previous transmural myocardial infarction, 4 with conduction defects, and 5 with ischemic changes in the ECGs. These patients demonstrated increased ventricular ectopy after the use of diuretics. Since the subgroups had been selected retrospectively and because of the small number of subjects, larger trials are needed to confirm their observations.

Two additional studies were published in a single report during the progress of the MRC trial of Great Britain.³⁷ In the first study, an increased incidence of ventricular ectopy was found in a group of thiazide-treated patients. Because these patients lacked a baseline control recording, a second study was undertaken that monitored the ECG change before and after treatment with thiazides. This study failed to reveal any difference in the frequency of ventricular ectopy before and after treatment, nor was there any correlation between potassium serum levels and arrhythmic activity. More importantly, the complete MRC trial indicated no essential difference in death rates due to CHD in thiazide-treated patients compared with controls.¹⁹

In a more recent study using ECG monitoring,³⁸ the frequency of ventricular arrhythmias of all grades was found to be increased in hypertensive patients with left ventricular hypertrophy as compared with those without hypertrophy. However, various arrhythmias, including ventricular tachycardia, were not associated with diuretic therapy or hypokalemia.

Further evidence regarding the lack of correlation between diuretic-induced hypokalemia and ventricular arrhythmias is provided by investigators for the Glasgow Blood Pressure Clinic, who reported on 3783 hypertensive patients followed up for an average of 6.5 years.³⁹ In patients treated with diuretics, the average level of serum potassium was the same in those who died of ischemic heart disease (3.71 mmol/L) as in those who survived (3.72 mmol/L). Although CHD mortality was high regardless of treatment, the authors concluded that thiazide-induced hypokalemia was not associated with the increased risk.

MAGNESIUM AND POTASSIUM

Magnesium is a coenzyme in the activation of sodium-potassium-adenosine triphosphatase. This substance supplies energy to the sodium-potassium-membrane pump, which is important in maintaining the gradient between extracellular and intracellular sodium and potassium.⁴⁰ In the kidney, magnesium is largely resorbed in the loop of Henle.⁴¹ Thiazide diuretics that act in the early distal tubules have only a minor effect on magnesium excretion in comparison with loop diuretics.

Correlation between extracellular and intracellular

changes in magnesium or potassium as caused by various interventions is poor,⁸ and, therefore, many investigators have used muscle biopsies or leukocytes for measurements of intracellular magnesium and, in the case of potassium, total-body measurements as well. There is, however, a high correlation between the intracellular content of magnesium and potassium. Decreased content of magnesium within cells is often found in patients with reduced intracellular potassium.⁴²

There have been several reports of reduced intracellular magnesium and potassium levels measured directly in patients receiving diuretics.⁴³⁻⁴⁴ However, the review of total-body potassium measurements as indicated above⁵ found negligible deficiencies of total-body potassium during long-term treatment with diuretics. Furthermore, other studies of leukocyte and muscle content of these ions during treatment with various diuretics indicate negligible reductions of 4% to 6% in intracellular potassium or magnesium.^{45,46}

The difference between results of the first group of studies indicating deficiency of intracellular potassium and magnesium and the second group showing no or only insignificant reduction seems to be due to the type of patients studied. The patients in the first group who showed intracellular deficits had, with few exceptions, congestive heart failure in addition to taking diuretics.⁴³⁻⁴⁴ Patients in the second group^{45,46} who received diuretics were normal or had essential hypertension uncomplicated by overt heart disease. Although Dyckner and Wester⁴⁴ included a few patients with uncharacterized hypertension, they were not reported on separately from the heart failure patients, and so results for the hypertensive subgroup could not be assessed.

Patients with congestive heart failure exhibit reductions in total-body potassium even in the absence of treatment with diuretics.⁴⁷⁻⁵¹ For example, none of Aikawa and Fitz's⁴⁷ patients received oral diuretics. White et al⁴⁸ found no correlation between the duration of diuretic therapy and the amount of potassium depletion. Furthermore, four patients without diuretic treatment exhibited similar depletion of total-body potassium. These results were confirmed by Flear et al.⁴⁹ Because these investigators used total-body measurements, the reduction in patients with congestive heart failure without diuretics could be due to muscle wasting and loss of cell mass, rather than to absolute cellular deficits of potassium. However, as early as 1930, long before the advent of thiazide diuretics, Harrison et al⁵⁰ found reduced potassium content in skeletal and cardiac muscle in patients with congestive heart failure. Also, before the availability of oral diuretics, their observation was confirmed by Iseri et al⁵¹ by direct tissue analysis of muscle both in patients with congestive heart failure and in those with MI. Both of these studies used tissues obtained at autopsy, and it is known that potassium loss occurs from cells after death. However, the potassium content was markedly lower than that of control autopsy samples obtained from patients dying suddenly from illness unattended by fluid or electrolyte disturbance. Similar results in congestive heart failure before the advent of oral diuretics were reported by Cort and Mathews⁵² in 1954 with the use of balance studies as well as biopsy specimens of living striated muscle. The extent of intracellular potassium depletion was similar to that reported by modern investigators who studied patients with congestive heart failure who were receiving oral diuretics.^{8,41-45} These results indicate that the potassium deficit is due primarily to alterations associated with congestive heart failure per se and is characterized by an absolute reduction in the potassium content of muscle cells rather than loss of cell mass alone. It is possible that diuretics may increase the potassium deficiency to a minor degree.

In patients with congestive heart failure, administration of potassium failed to restore the intracellular deficit, whereas

administration of magnesium increased intracellular potassium levels.⁴⁴ Potassium-sparing diuretics also restored potassium stores in patients with congestive heart failure.⁴¹ Treatment of cardiac patients with magnesium or potassium-sparing diuretics would, therefore, seem to be desirable. However, there is insufficient evidence of intracellular potassium deficits in patients with uncomplicated hypertension^{6,45,46} to justify replacement therapy in diuretic-treated patients who do not have major cardiac complications.

ACUTE MI

It is well known that excess catecholamines can produce hypokalemia.⁵⁸ Acute MI is often accompanied by increased catecholamine levels, resulting in hypokalemia,⁵⁴ the severity of both being related to the extent of the infarct. The hypokalemia can occur in the absence of diuretics.⁵⁶ Although thiazide-induced hypokalemia may not cause arrhythmias in hypertensive patients with normal hearts, it possibly could increase the risk of fatal arrhythmias in the presence of myocardial ischemia associated with an acute MI. However, the majority of the long-term hypertension trials cited above do not indicate that the ratio of fatal to nonfatal MI is any higher in the thiazide-treated patients than in the control groups. This suggests that an acute MI occurring in a thiazide-treated patient poses no greater risk of a fatal outcome than an MI developing in a patient who is not receiving thiazide.

The relationship between hypokalemia and ventricular arrhythmias during the early symptomatic phase of acute MI is complicated by the presence of excessive sympathetic nervous system activity and production of catecholamines. Catecholamines reduce serum potassium levels acutely and increase the hypokalemic effect of thiazides,⁵⁶ but, unlike diuretics, catecholamines also increase the incidence of ventricular arrhythmias independent of their hypokalemic effect.⁵⁹ Thus, hypokalemic blood samples drawn relatively early after an MI may be without causal significance but act merely as a marker for the presence not only of diuretics but also of excessive catecholamines associated with the pain and stress of the infarct. Arrhythmias developing during this hypokalemic period may be due to the direct arrhythmogenic effects of catecholamines on the myocardium, or to tissue anoxia, myocardial cell injury, or a multitude of factors other than the hypokalemia per se.

Nordrehaug et al⁶¹ found that plasma potassium levels taken early at an average time of 3.8 hours after the onset of an MI were inversely related to the ventricular tachycardia. Dyckner et al⁶² found a similar relationship in the early period after an MI. However, Nordrehaug et al found that patients receiving diuretics at the time of the infarct had no significant association with the degree of ventricular ectopic activity, suggesting that other factors, such as increased catecholamine levels rather than diuretics, were causing the ventricular arrhythmias. Furthermore, another study by Nordrehaug⁶³ indicated that low potassium values drawn 8 hours after the onset of an MI (when catecholamine levels are lower) were not associated with an increased incidence of ventricular tachycardia. Thus, the increased arrhythmias observed during the first few hours after the infarct may well have been due to the direct myocardial effects of an associated increase in catecholamines, and the hypokalemia may have been an incidental rather than the causal factor.

If the arrhythmias associated with acute MI are indeed related to hypokalemia, the correction of the latter with potassium infusions should reduce the incidence of such rhythm disturbances. So-called polarizing solution, which contains potassium along with glucose and insulin, was extensively used in the past in the treatment of acute MI. However,

raising the potassium level back to normal in acute MI with polarizing solution had no significant effect on the ventricular arrhythmias.^{60,66} This result is consistent with the concept that factors other than a low serum potassium level are the probable causes of fatal arrhythmias in MI.

THE RELATIONSHIP OF DIURETICS TO SERUM CHOLESTEROL LEVEL

Critics of the diuretics claim that if thiazide-treated patients manage to escape fatal arrhythmias over the intermediate term, they will still be at risk of aggravated CHD atherosclerosis over the long term because thiazides raise serum cholesterol level. However, this argument is not supported by the long-term trials described below.

Increase in serum cholesterol level after administration of thiazide diuretics was first observed by Schoenfeld and Goldberger⁶¹ in 1964. This and other reports passed largely unnoticed until 1976, when Ames and Hill⁶² published their report demonstrating a rise in serum cholesterol level during diuretic treatment of hypertensive patients. However, the period of treatment was relatively short compared with that in most later studies, as shown in Table 2. Three studies exhibited modest elevation of serum cholesterol level, the longest in duration (1 year) being the Veterans Administration-National Heart, Lung, and Blood Institute (Bethesda, Md) trial. None of the three trials⁶²⁻⁶⁴ exhibited an average increase of more than 0.28 mmol/L.

By contrast, seven trials^{17,24,65-69} indicated essentially no change or a decrease in serum cholesterol level after long-term treatment (Table 2). In six of the seven trials, patients were treated with diuretics for 2 to 6 years. In the HAPPY trial, there was no change in serum cholesterol level from baseline after 1 year.¹⁷ In the MRC trial, there was a negligible rise in cholesterol level averaging 0.03 mmol/L and a minimal fall in the placebo group.⁶⁷ The other six long-term trials found either no change or a fall in serum cholesterol level.

Over the long term, serum cholesterol level fell somewhat more in the control than in the intensively treated groups in the MRFIT⁶⁸ and HDFP⁷⁰ trials. However, the actual differences were small, averaging 0.11 mmol/L in MRFIT and 0.10 mmol/L lower in the control group than in the experimental group. After 45 months in the HAPPY trial,¹⁷ the β -blocker group averaged 0.12 mmol/L lower than the thiazide-treated group, while after 3 years in the MRC trial⁶⁷ the placebo group averaged 0.18 mmol/L less than the thiazide-treated group. On the other hand, in the European Working Party on High Blood Pressure in the Elderly trial,⁶⁵ after 3 years the decrease in serum cholesterol level averaged 0.09 mmol/L more in the treated group than in the placebo controls. While there was a trend toward slightly less long-term fall in cholesterol level in the treated patients in four of these five trials, the differences were sufficiently small to be of questionable clinical importance.

Freis and Materson⁷¹ were among the first to emphasize that the moderate elevation in serum cholesterol level is a short-term effect. Further evidence is provided by three trials that assessed the changes in serum cholesterol level after both short-term and long-term treatment with diuretic (Table 2). The results were the same in all three trials.^{70,72-74} Serum cholesterol level rose during the short term of 1 to 12 months and then fell to slightly below baseline at 1 to 5 years. The Veterans Administration study on propranolol vs hydrochlorothiazide as primary monotherapy^{72,73} followed up 147 patients taking hydrochlorothiazide alone for 1 year. After 10 weeks of therapy with hydrochlorothiazide alone, serum cholesterol level averaged 0.16 mmol/L above the pretreatment level. After 1 year of treatment, however, serum cholesterol

Table 2.—Changes in Serum Cholesterol Level With Short-term vs Long-term Treatment of Hypertension With Diuretics*

Trial	No. of Patients	Diuretic and Dose, mg	Duration of Treatment	Average Change in Cholesterol, mmol/L
Trials Indicating a Rise in Cholesterol				
Ames and Hill ⁶²	74	Chlorthalidone, 25-100	1-3 mo	+0.28
VA-NHLBI ⁶³	302	Chlorthalidone, 50-100	1 y	+0.26
Grimm et al ⁶⁴	57	Chlorthalidone, 100, or hydrochlorothiazide, 100	6-12 wk	+0.18
Studies Indicating No Change or a Fall in Cholesterol				
EWPH ⁶⁵	190	Hydrochlorothiazide, 25-50	2 y	-0.52
Framingham ⁶⁶	288	Thiazides	2 y	-0.16
MRC ⁶⁷	17354	Bendroflumethiazide, 10	3 y	+0.05†
MRFIT ⁶⁸	1021‡	Chlorthalidone or hydrochlorothiazide, 50-100	6 y	-0.23
MPPCD (Helsinki, Finland) ²⁴	1203	Hydrochlorothiazide, 50	5 y	0
Oslo ⁶⁹	300	Hydrochlorothiazide, 50	3 y	0
HAPPY ¹⁷	6669	Bendroflumethiazide, 5, or hydrochlorothiazide, 50	1 y	0
Trials Indicating an Early Rise Followed by a Fall Below Baseline				
VA propranolol-hydrochlorothiazide ⁷²	147	Hydrochlorothiazide, 50-200	10 wk	+0.16
VA propranolol-hydrochlorothiazide ⁷³	147	Hydrochlorothiazide, 50-200	1 y	-0.08
Alcazar et al ⁷⁴	236	Hydrochlorothiazide, 50-100	1-3 mo	>0§
			1-2 y	<0§
HDFP ⁷⁰	7006	Chlorthalidone, 50	6-12 mo	+0.10
			2-5 y	-0.23

*VA indicates Veterans Administration; NHLBI, National Heart, Lung, and Blood Institute (Bethesda, Md); EWPH, European Working Party on High Blood Pressure in the Elderly; MRC, Medical Research Council of Great Britain; MRFIT, Multiple Risk Factor Intervention Trial; MPPCD, Multifactorial Primary Prevention Trial of Cardiovascular Disease in Middle-Aged Men; HAPPY, Heart Attack Primary Prevention in Hypertension trial; and HDFP, Hypertension Detection and Follow-up Program.

†Considered essentially unchanged from baseline.

‡Number of patients with special interventions who received diuretics only.

§Numerical value of changes not given; $P < .01$.

level averaged 0.08 mmol/L below the baseline mean. In a study of 236 hypertensive patients treated by Alcazar and his associates⁷⁴ with 50 to 200 mg of hydrochlorothiazide per day, serum cholesterol level rose significantly during the first 3 months of treatment but fell significantly after 1 to 2 years. The HDFP reported similar results.⁷⁰ Serum cholesterol levels averaged 0.10 mmol/L higher in the first 6 to 12 months of diuretic treatment and then fell after 2 to 5 years to an average value 0.23 mmol/L below the baseline level.

CONCLUSIONS

The opinion that diuretics increase the risk of fatal CHD has not been confirmed by the accumulated evidence. When all of the relevant data, rather than selected elements, are taken into account, it becomes evident that there is little to support the hypothesis that diuretics have cardiotoxic properties. In particular, the data from MRFIT that initiated the charges against diuretics cannot withstand close scrutiny because of the intrinsic weakness of the study's methods as well as the contradictions of its findings.

The principal evidence in MRFIT was that in patients with minor ECG abnormalities at entry, there were more CHD deaths in the special intervention group than in the usual care group. They suggested that this unfavorable effect could be due to the greater use of thiazide diuretics in the patients in the special intervention group. However, such evidence based on retrospective subgroup analysis is known to be unreliable; furthermore, in the subgroup of patients with abnormal exercise ECG tests at baseline, the results were the opposite, with 57% more CHD deaths occurring in the usual care group than in the special intervention group. There are still other criticisms of the MRFIT data, as described in the body of the review, that further weaken their argument that

thiazide-induced hypokalemia causes increased CHD mortality.

Of 12 published morbidity-mortality trials in hypertension using thiazides among other drugs, only 2 experienced more deaths in the diuretic-treated patients than in controls, neither of the differences being significant. These were the Oslo study and the MAPHY trial. However, the results of the Oslo study were impaired by the low incidence of CHD events, while the MAPHY trial represents a subgroup of the larger HAPPY trial, which had found no difference in total CHD mortality between diuretic-treated and β -blocker-treated patients. The remaining 10 trials, including total patients in MRFIT, uniformly found no evidence for diuretic-induced CHD deaths or other cardiovascular mortality.

Another retrospective subgroup analysis of minor resting ECG abnormalities carried out by HDFP could not confirm the principal findings of MRFIT that diuretics increased cardiovascular mortality.

Recent evidence from 24- to 48-hour monitoring of ECG changes does not indicate any increase in ventricular arrhythmias during thiazide treatment either in the presence or absence of hypokalemia or in patients with left ventricular hypertrophy. Early reports indicating ECG changes have not been confirmed. Furthermore, a causal relationship between thiazide-induced hypokalemia and fatal arrhythmias in patients with acute MI has not been proved.

Intracellular magnesium and potassium deficiency may occur in patients with congestive heart failure even in the absence of diuretics. However, the intracellular content of these electrolytes is not reduced by diuretics in hypertensive patients who do not have major cardiac complications.

Finally, studies of long-term treatment with thiazide diuretics indicates that the modest elevation of serum cholesterol

level is transient and subsides back to or below the baseline after approximately 1 year of treatment. Minor trends toward lesser long-term reductions in serum cholesterol level in thiazide-treated compared with control patients have been reported. The differences are small, however, and their clinical significance appears questionable.

IMPLICATIONS WITH RESPECT TO CLINICAL TREATMENT OF PATIENTS

Diuretics are important in the treatment of hypertension. Their mode of action in reducing blood pressure by volume depletion is unique and represents an important mechanism for lowering blood pressure in the majority of patients.

Thiazides in adequate therapeutic doses will control blood pressure in approximately half of the patients^{72,73} (somewhat more in blacks and the elderly and somewhat less in young whites), and adding a second drug such as a β -blocker or a converting enzyme inhibitor will increase the percentage controlled to about 80% to 90%. Because of this considerable antihypertensive effectiveness and low cost, it is of importance for the physicians to know the actual toxic potential of the diuretics.

In the medicolegal climate of today, many physicians practice defensive medicine. Widespread publicity of suspected cardiotoxic effects has greatly affected the sales of diuretics. Another recent trend is reduction in dosage of diuretics sometimes to levels that may not be effective in many patients.^{75,76} Thus, the omission or reduction of dosage of diuretics may hinder effective treatment as the physician is forced to substitute much more costly and sometimes less effective drugs.

The above considerations apply to the huge population of patients with uncomplicated hypertension. This is not to deny that there are individual patients who would be better treated with other drugs, such as β -blockers in those who have sustained an MI or converting enzyme inhibitors in those receiving digitalis. Diuretics elevate blood glucose and uric acid levels and may precipitate diabetes mellitus or gout in a few predisposed individuals. Nevertheless, diuretics would seem to be safe and effective in the great majority of hypertensive patients who do not present such special problems.

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